

The dental perspective on metformin

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Cite this article: Yollar ET. The dental perspective on metformin. *Ank Med J.* 2024;3(4):92-95.

Received: 04.06.2024

Accepted: 12.07.2024

Published: 23.07.2024

ABSTRACT

Metformin is a safe, non-toxic and well-tolerated drug most commonly prescribed for the treatment of diabetes. Additionally, metformin is a drug that has been reported to be used in the treatment of liver and kidney disorders and bone disorders, as well as in the treatment of diabetes. It has become popular in the field of dentistry with the discovery of the odontogenic, osteogenic and angiogenic effects of metformin in recent studies. With these properties, metformin was combined with many substances used in dentistry and its effects on teeth and surrounding tissues were examined. The purpose of this review is to provide an overview of the studies conducted with metformin in the field of dentistry.

Keywords: Metformin, odontogenic, osteogenic, dentistry

INTRODUCTION

Millions of diabetics take metformin as their first course of treatment for type 2 diabetes mellitus (T2DM).¹ It is secure, non-toxic, and well tolerated in its role as an insulin sensitizer.¹⁻³ By reducing gluconeogenesis in the liver, glucose absorption in the small intestine, and the production of free fatty acids in adipose tissue, metformin lowers blood glucose levels and increases glucose uptake by muscle.⁴ Metformin has been examined for its ability to reduce blood sugar levels as well as for its cardiovascular system protection and anti-cancer properties in various malignancies.⁴⁻⁶ According to Kim et al., the radiation sensitizing action of Metformin on hepatocellular carcinoma is caused by an increase in DNA degradation, cell cycle arrest, and apoptosis.⁷

Benefits of metformin have been documented in the treatment of liver illnesses,^{8,9} renal damage and disorders,¹⁰ neurodegenerative diseases¹¹⁻¹³ and bone abnormalities,¹⁴ depending on the patient profile and different disease circumstances. Metformin has a number of important features that researchers have looked into ways to enhance. These properties include the potential for odontogenic, osteogenic, and angiogenic differentiation, which have a number of potential clinical uses.¹⁵⁻¹⁷ Metformin can enhance osteoblast development of MSCs (mesenchymal stem cells) employed in tissue regeneration, according to in vitro and in vivo investigations.^{15,18} This review aims to provide an overview of the various benefits of metformin and its uses in dental treatments.

MECHANISM OF EFFECT OF METFORMIN

Metformin's main target in eukaryotic cells is complex-I of the electron transport chain, which results in an accumulation of ROS (Reactive oxygen species) and oxidative damage to lipids, proteins, and DNA and can enhance the effects of ionizing radiation.^{19,20} The initial energy conversion complex of several respiratory chains in eukaryotic cells, Complex-I (proton-pumping NADH), sets up the proton motive force necessary for energy-consuming pathways. The respiratory chain has complex-I homologues for many microorganisms.^{21,22}

Metformin's suppression of complex-I causes eukaryotic cells to use less oxygen and produce less adenosine triphosphate (ATP). Adenosine monophosphate (AMP) levels rise in eukaryotic cells as a result of the reduction in ATP generation, and the energy sensor AMP-activated kinase (AMPK) is activated.²⁰ Two regulatory subunits (a and b) and a catalytic subunit (a) make up the serine/threonine protein kinase known as AMPK.²³

AMPK is activated and AMP concentrations rise in response to dietary restriction, hypoxia, and metformin treatment when ATP concentrations are low.²⁴ Neutrophils or macrophages are more effective in killing bacteria when AMPK is activated. Innate immune responses that include the phagocytosis of microorganisms in the presence of neutrophils and macrophages are essential for regulating inflammation.²⁵

STUDIES IN DENTISTRY WITH METFORMIN

Metformin-containing resins were found to be promising in a study by Wang et al. for a wide range of dental applications, including deep caries and exposed pulp cavities, to encourage DPSCs (dental pulp stem cells) to synthesize new dentin and protect the pulp.²⁶ In a different study by Houshmand et al., metformin promoted osteogenic differentiation of dentin pulp stem cells in osteogenic medium, while metformin did not produce differentiation in conventional medium.²⁷ The odontogenic differentiation of dental pulp stem cells was greatly boosted by the addition of metformin to the calcium phosphate cement-chitosan composite, according to research by Qin et al., without impairing cell survival or proliferation.²⁸

According to the findings of the study by Boreak et al.,²⁹ pretreatment with metformin increased the angiogenic ability of the DPSC secretome as seen by the growth of quaternary blood vessels in the chick embryo yolk sac membrane model after treatment with the DPSC secretome. The creation of vascular tubules in 3D cultures demonstrated that the use of a serum-free culture medium generating growth factors such as B27, heparin, and VEGF-A (Vascular Endothelial Growth Factor-A) improved the ability of DPSC for vasculogenesis.³⁰ Qin et al.¹⁶ believed that metformin could play a significant pharmacological role in triggering odontoblastic differentiation and offer new perspectives for the treatment of pulp exposure in an in-vitro study that sought to investigate the effects of metformin on the proliferation and differentiation of DPSCs.

Farnaz et al. found that 100 Mol/L metformin boosted dental pulp stem cell viability in their preliminary study evaluating the effects of metformin on both proliferation and osteogenic capacity of dental pulp stem cells cultivated on freeze-dried bone allograft granules. Metformin has also been demonstrated to improve dental pulp stem cell survival when cultivated on freeze-dried bone allograft granules.³¹ Zhang et al. employed the CCK-8 assay to assess the proliferation potential of young and elderly DPSCs treated with different concentrations of metformin (10, 50, 100, 250, and 500 M) in order to choose the metformin concentration to be used in the investigations. It has been demonstrated to inhibit and promote DPSC growth.³²

Dental professionals may use photodynamic therapy to treat and diagnose malignancies and mouth infections. A viable substitute for antibiotics that are more likely to develop resistance to the oral bacterial flora may be offered by photodynamic therapy's antibacterial function.³³ In the study of Afrasiabi et al., they found that the use of metformin in combination with photodynamic therapy would increase the effectiveness of photodynamic therapy and thus lead to its potential effect in reducing periodontal infections.³⁴

The tumor of epithelial origin known as oral squamous cell carcinoma (OSCC) is malignant and aggressive, and it is now one of the leading causes of cancer-related fatalities.³⁵ Although there are many different treatment options, including surgery, chemotherapy, and radiotherapy, none have been proven to increase survival rates. A trustworthy therapeutic substance is urgently required for the detection

and growth suppression of cancer cells.³⁶ MF has proven to have promising anti-cancer capabilities in the search for a workable agent.

The potential of metformin to target PI3K/mTOR (Fosfatidilinositol 3-kinaz/ Mammalian Target of Rapamycin) signaling for the prevention of head and neck squamous cell carcinoma was examined in a single-arm, open-label phase IIa clinical trial in patients with oral premalignant lesions by Gutkind et al. Clinical examination and biopsy were performed both before and after therapy on people with oral premalignant lesions who were otherwise healthy and did not have diabetes. For 12 weeks, participants took metformin. Blood, saliva, and pre- and post-treatment biopsies were collected for various biomarker studies. The results of this study support further research into metformin as a chemopreventive drug by showing that it increases histological responses and modulates the mTOR pathway when administered.³⁷

According to the study by Liu et al. examining the effect of metformin on oral squamous cell carcinoma (OSCC) and the underlying processes, metformin reduced oral squamous cell carcinoma growth.³⁸

Pyruvate dehydrogenase levels were assessed in patients with oral squamous cell carcinoma and oral dysplasia in the study by Guimares et al., which sought to determine the effects of metformin in hypoxic circumstances. To examine metformin's effectiveness in the presence of hypoxia, it was given intravenously. An oral squamous cell carcinoma cell line model showed that metformin decreased cell growth and migration.³⁹

Locally applied metformin as an aid to scaling and root planing has been proven to be more advantageous than scaling and root planing alone in the treatment of periodontal abnormalities because of the significant role that metformin plays in bone growth and immunomodulatory function.³⁹ Better treatment outcomes for intraosseous defects have been observed in numerous clinical trials using different metformin gel doses.^{40,41}

Five groups of twenty one rats each were randomly assigned to the Arajo et al. study to examine the effects of metformin on inflammation, oxidative stress, and bone loss in a rat model of ligature-induced periodontitis. The rats received different doses of metformin as well as metformin with and without ligatures for 10 days. It was determined that rats with ligature-induced periodontitis experienced less inflammation, oxidative stress, and bone loss when treated with metformin at a dose of 50 mg/kg.⁴²

In the study of Kominato et al. to investigate the effects of metformin on gingival wound healing in insulin-resistant prediabetes, mice were fed a normal diet or a high-fat diet for 10 weeks; Half of the high-fat diet mice were treated with metformin (high-fat diet + met) for the past 2 weeks. Insulin and glucose tolerance tests were performed. The palatal gingiva (2.0 x 0.5 mm) was surgically removed adjacent to the maxillary molars. Postoperative wound closure was evaluated histomorphometrically for 1 week.

The mRNA expression of VEGF and endothelial nitric oxide synthase (eNOS) in tissue was measured by real-time polymerase chain reaction. In vitro proliferation and migration of human gingival fibroblasts cultured under high glucose or control conditions with/without metformin were analyzed. Metformin improved delayed gingival wound healing in insulin-resistant prediabetes by accelerating HGF (Hepatocyte growth factor) proliferation and migration through Akt phosphorylation in the insulin signaling pathway.⁴³

The effectiveness of host modulators combined with non-surgical periodontal therapy in lowering probing pocket depth in individuals with periodontitis was examined in the review by Donos et al. They came to the conclusion that there was promise for therapeutic application of the local bisphosphonate and metformin gels in subony deformities, but this needed to be verified.⁴⁴

Bak et al.⁴⁵ examined the impact of metformin on osteoblast, osteoclast, and adipocyte development as well as alveolar bone loss in ligate-induced periodontitis. They came to the conclusion that through promoting osteoblast development, metformin may have a positive impact on alveolar bone in periodontitis.

In the systemic review of Ikbar et al.,⁴⁶ they aimed to evaluate the efficacy of MF containing Platelet Rich Fibrin (PRF) alone on Platelet Rich Fibrin in the treatment of periodontal bone defects. They demonstrated the complementary benefits of MF + PRF combination therapy over monotherapy in resolving periodontal bone defects. The quest to achieve maximum regeneration in periodontal bone defects, combination therapies such as MF + PRF have been reported to be better treatment options than other modalities.

In order to treat subbone abnormalities in patients with chronic periodontitis, Patil et al.⁴⁷ conducted a clinical and radiographic comparison and evaluation of the efficacy of 1.5% MF gel and placebo gel as an addition to scaling and root correction (SRP) and curettes. Using 1.5% metformin topically improved the clinical results of curettage and standard treatment (SRP).

The ability of MF to have favorable impacts on orthodontic tooth mobility is another noteworthy feature. To show how MF affects orthodontic mobility, Sun and colleagues conducted a study on Wistar mice with induced T2DM (Type 2 Diabetes mellitus) in 2017. The experimental and control groups of rats received orthodontic appliances, and two weeks later, the outcomes were assessed. Histological evidence that MF lowers the probability of unintended orthodontic tooth movement is provided by the fact that MF-treated rats showed increased tooth movement with normal osteoclast levels. Additionally, MF reduced the expression of sclerostin and enhanced the immunolocalization of the dentin matrix protein.⁴⁸

Metformin monotherapy dramatically speeds up the osseointegration of intraosseous implants, according to studies in animal models. By blocking the negative effects of advanced glycation end products on osteoblastic cells, including interactions with receptors for advanced glycation

end products, metformin's effects on wound healing are essential for implant survival.⁴⁹

The utilization of stem cells from human exfoliated deciduous teeth (SHED) in tissue engineering and regenerative medicine is highly promising. According to research done in 2020 by Zhou et al., MF stimulates the AMPK pathway, which in turn induces osteogenic differentiation in SHEDs. It also has a beneficial impact on the production of osteogenic genes and proangiogenic growth factors in SHEDs.⁵⁰ According to a recent study by Deng et al., MF pre-treatment significantly increases the SHED-mediated angiogenesis in vivo of human umbilical endothelial cells in addition to promoting cell proliferation and inducing multiple forms of differentiation; these findings may pave the way for the use of SHEDs pre-treated with MF for tissue regeneration.⁵¹

CONCLUSION

Metformin can reduce inflammation, obesity, cardiovascular and renal illnesses, malignancies, polycystic ovarian syndrome, osteoporosis, and periodontitis, according to several cell culture research, animal studies, and clinical trials. Furthermore, it has been demonstrated that these effects involve a variety of molecular interactions. The advantages of metformin and its use in medicine are appropriate for dental procedures. To produce trustworthy evidence, however, it is probable to require repetitive and lengthy chapters. The precise dose and mode of action of metformin in dentistry can be ascertained by thorough in-vivo research.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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